Combine and Conquer

Minimizing the Impact of Toxicity Associated with Novel Immunotherapy-Angiogenesis Inhibitor Combinations

Renal Cell Carcinoma Tweetorial

References

CME Info
bit.ly/3VDaK81

1/ #OncTwitter #NephTwitter #TumorBoardTuesday
✅#RenalCell #MedTweetorial🧵
w @brian_rini @shilpaonc @katy_beckermann

🦺TKI/IO safety data
🥽Tox to look 4
⛑️AE mgmt

🆓#CME @BonumCE🔗bit.ly/3VDaK81
Support by edu grants from Eisai & @Merck

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🆓#CME info ➕ full ref list🗒️ 👉 bit.ly/3VDaK81

✳️The critical elements👇

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🟢 Which of the following TKI/IO combo regimens is 🚫NOT approved by the FDA for the frontline mgmt of #RenalCell carcinoma?

- ☐ Atezo + bev
- ☐ Pembro + axitinib
- ☐ Pembro + lenva
- ☐ Nivo + cabo

Ref #

1

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Ref # 1

💎Combo txs as SOC for 1st line mRCC💎

TKI/ICI combos:
- #lenvatinib (TKI) + #pembrolizumab (PD-1 mAb)
- #axitinib (TKI) + pembro
- #cabozantinib (TKI) + #nivolumab (PD-1 mAb)

Dual ICI combo:
- #ipilimumab (CTLA-4) + nivo

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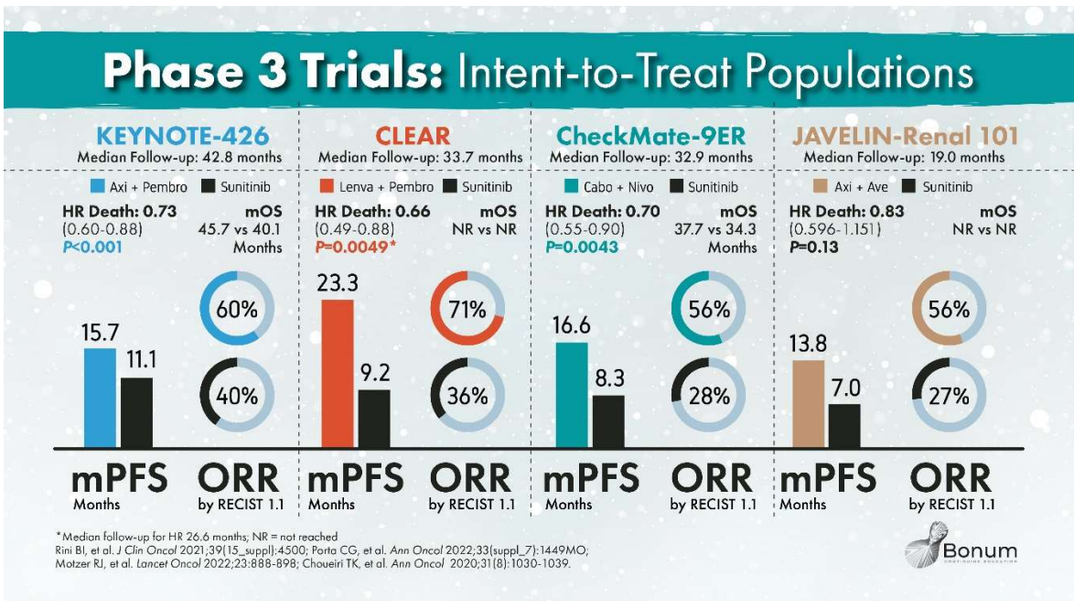
Ref # 2-5

🔑Ph3 trls #KEYNOTE426, #CLEAR, #CheckMate9ER, #CheckMate214

💎Each combo regimen ⬆PFS, OS, & ORR vs sunitinib
💎Axi-avelumab approved but OS data immature
💎Benefit across IMDC risk groups
💎Axi-pembro=longest f/u among approved TKI-ICI in RCC



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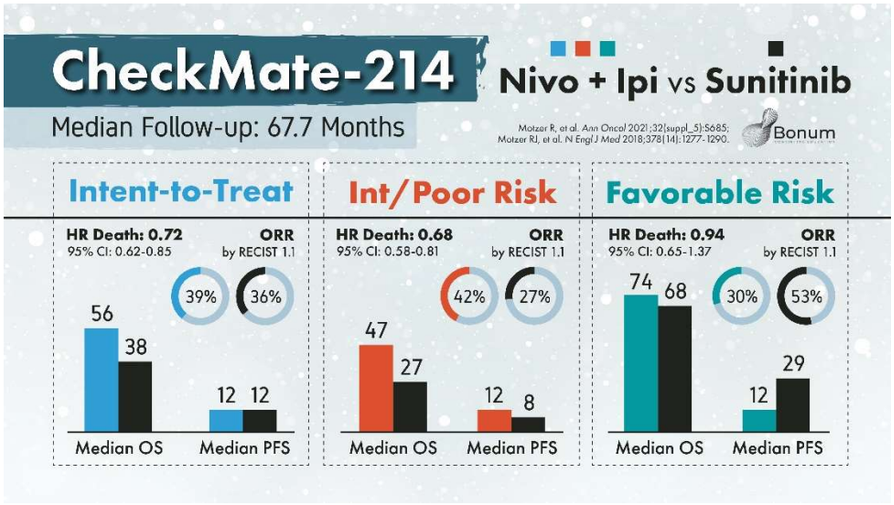
Ref # 1, 6, 7

✳️Dual ICI combo (ipi + nivo) also approved tx option

💎#CheckMate214 - ipi + nivo vs sunitinib
✅Longest follow-up in frontline RCC (>5 years)
✅OS and PFS favor combo tx in int/poor risk pts



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Ref # 8

🟢Which of the following is a characteristic feature of the most common toxicities associated with anti-angiogenic therapies?

- ☐ Delayed presentation
- ☐ Dose-dependent
- ☐ Irreversible
- ☐ Unpredictable

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Ref # 8-11

Combo tx =possible⬆️tox➡️can lead to trtmnt🛑

✨Anti-angio inhibitors=multi🎯TKIs
✨AEs related to shared 🎯s (e.g. VEGFR)=predictable class tox
✨Some nuance due 2 diff🎯/potency
✨Typ occur 1st few wks of ▶️tx
✨Broadly dose-dependent

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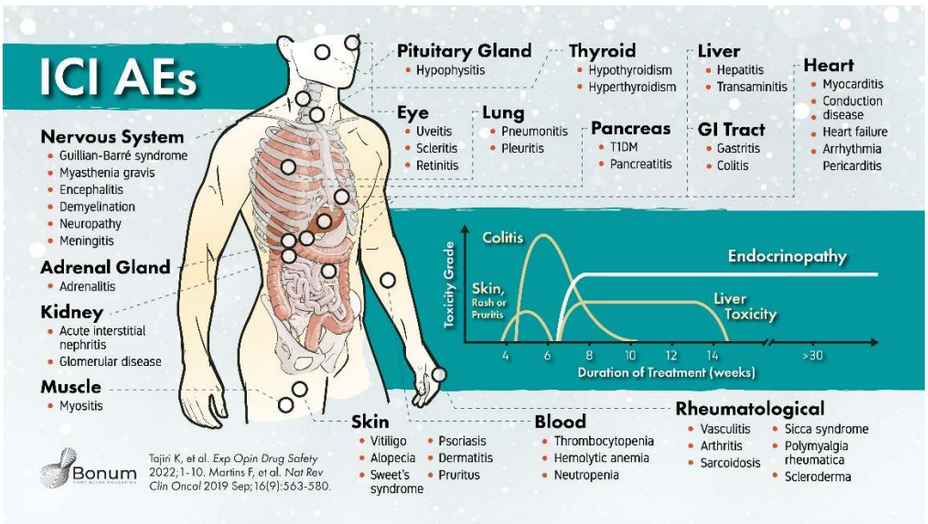
Ref # 12-15

ICI AEs related to immunostimulatory MOA (irAEs)
✳️Most mild/mod severity & reversible
⚠️CAN become sev/fatal if not promptly Dx & Tx⚠️
👉Impact virtually any bodily system
🗓️Most occur "early" (<14wks after start tx), some can occur mos/yrs later



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Ref # 8

🟢Which of the following is an AE that is commonly observed with both ICIs and TKIs?

- ☐ Diarrhea
- ☐ Hypertension
- ☐ PPES
- ☐ Stomatitis

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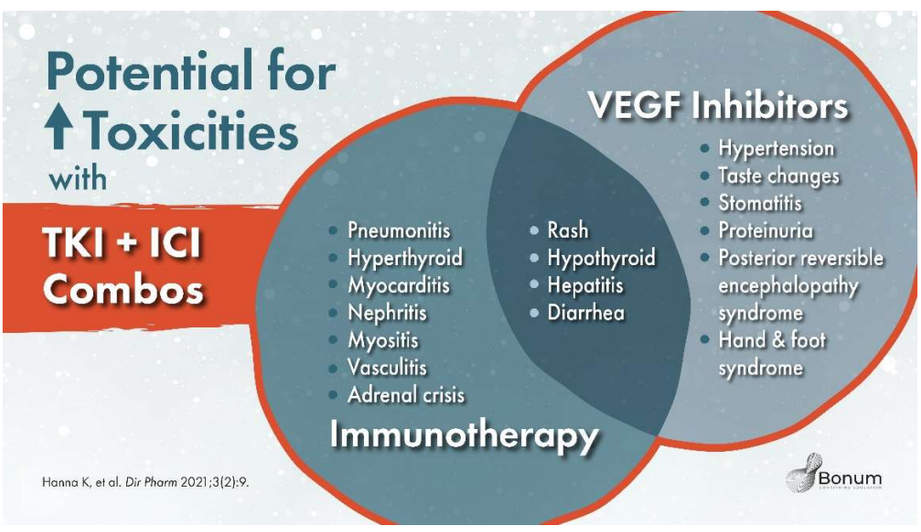
Ref # 8, 16-17

Some AEs attributable to either drug
These 🔁 overlapping tox can complicate pt mgmt



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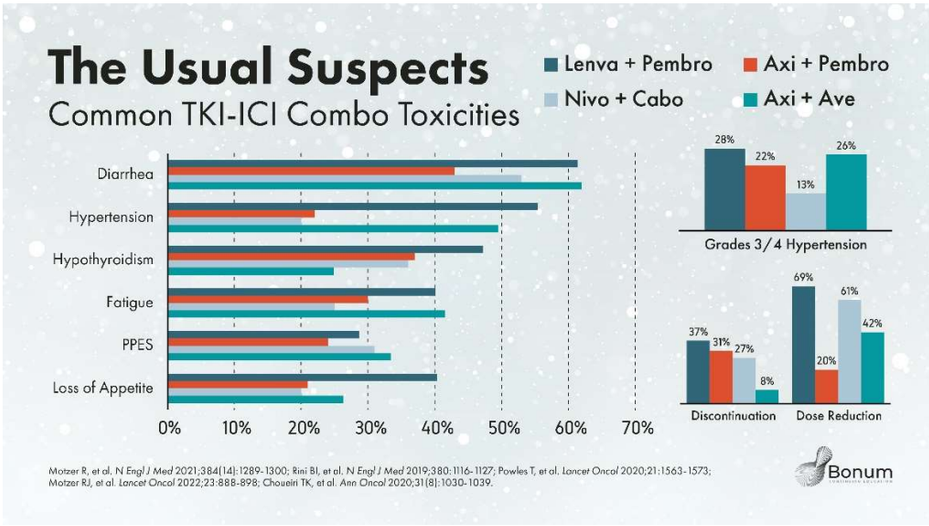
Ref # 4-5, 18-20

🔬Common tox in pivotal Phase 3 trials of TKI-ICI combos🔬
#KEYNOTE426 #CLEAR #CHECKMATE9ER #JAVELINrenal101

- Diarrhea
- HTN
- Hypothyroidism
- Fatigue
- PPES
- Loss of appetite



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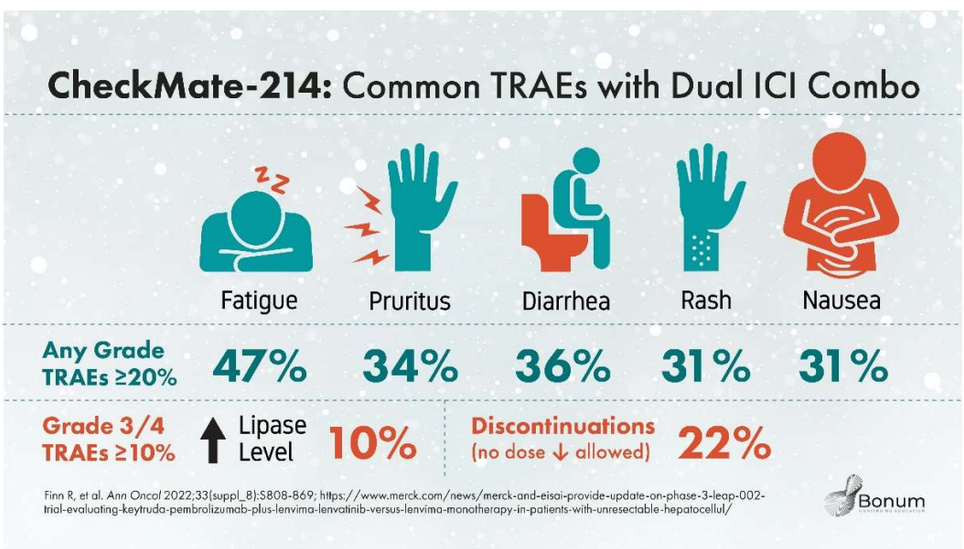
Ref # 6-7

🔬Common tox in pivotal P3 #CHECKMATE214 trial of dual ICI combo🔬

- Fatigue
- Pruritus
- Diarrhea
- Rash
- Nausea



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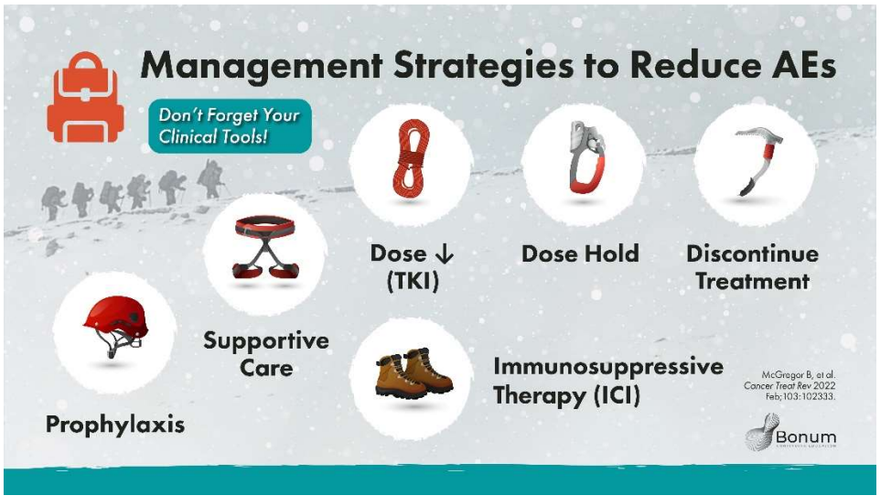
Ref # 15-16, 21

Effective tox mgmt ➡️optimize pt outcomes✅

🩺 Mgmt strategies include...🩺
- Prevention
- Monitor BP, urine protein, thyroid & liver function
- Dose modification (⏸️⬇️🛑)
- Supportive care



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Ref # 22

🟢Pt w mRCC
- Initiated tx w pembro + lenva
- Developed G3 diarrhea
- Lenva withheld & anti-diarrheal treatment initiated
- Diarrhea now resolved.

🟢What next step is best for the pt?

- ☐ Discontinue lenva
- ☐ Continue to hold lenva
- ☐ Resume lenva 14mg
- ☐ Resume lenva 20mg

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Ref # 22-25

If tox occurs, 🔑strategy
- ⬇️dose TKI
- Dose flex of TKIs>ICIs
- Axi fastest washout (hrs)

- Lenva 14mg➡️10mg ➡️8mg
- Axi 5mg➡️3mg➡️2mg
- Cabo 40mg QD➡️20mg QD➡️20mg QOD

Many pts need dose⬇️
BUT most can stay on tx if manage pt expectations

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🔬Research needed to ⬇️ tox while maintaining efficacy

❓Alternative dosing strategies (incl. dose breaks)
❓Effects of dose ⬇️ on pt outcomes
❓Effects of reduced ▶️ dose on pt outcomes

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Ref # 26

❓Effects of reduced ▶️ dose on pt outcomes

Limited prospective trial data to date: lenva 14mg ▶️ dose

🔸 Lenva 14mg vs 18mg + pembro in EC ➡️14mg ▶️ dose⬇️AEs & maint efficacy

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Ref # 1, 27

Plethora of options… ❓Which combo to pick ❓
Lack H2H trials or reliable biomarkers∴choice based on clin features & other factors, including:

🔸Tumor burden
🔹Comorbidities
🔸Pt age/func status
🔹Physician/pt pref
🔸QoL

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Ref # 6-7, 27

💡Examples for treatment selection💡
⛏️High tumor burden➡️ICI/TKI➡️short⏱️to response/deep responses

⛏️Older/frail pt➡️axi-pembro➡️greatest flexibility in dosing to avoid AEs

⛏️Uncontrolled HTN/CHF➡️ ipi-nivo➡️TKIs contraindicated

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Ref #

28

21/#TumorBoardTuesday
🔮Is triplet tx the future?
#COSMIC313=nivo + ipi + cabo int/poor-risk
#RenalCell

3x tx sig⬆️PFS vs pbo+nivo+ipi (mPFS: NR vs 11.3mos)
🚫⬆️OS - follow-up ongoing
Sig ⬆️in tox - G3/4 TRAEs in 73% pts vs 41% for pbo arm
TRAEs leading to tx🛑:12% vs 5%

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🔑Points
🔸TKI/ICI combos SOC 1L met #RenalCell
🔹⬆️PFS, OS & ORRs vs sunitinib all risk groups
🔸⬆️risk tox & potential 4 o'lap tox complicates pt mgmt
🔹Addl options incl axi-ave, dual ICI combo, & TKI monotx
🔸Choice guided by pt- & diz-specific factors

Claim your CME credit by completing the post-survey and evaluation. Link provided👉

📎 bit.ly/3VDaK81

📚 References 👇

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